Effective Health Care

Screening and Management of Pulmonary Hypertension in Adults with Sickle Cell Disease

Results of Topic Selection Process & Next Steps

The nominator, the American Society of Hematology (ASH) is interested in an AHRQ evidence review to inform the creation of clinical practice guidelines on screening and managing pulmonary hypertension (PH) in adults with sickle cell disease (SCD). This includes whether the use of right heart cardiac catheterization should be the preferred method of confirming a diagnosis of PH, and the effectiveness of various treatment options for PH. The ASH plans to use an AHRQ evidence review to inform their guidelines for managing PH in the SCD population.

Because there is limited original research addressing the key questions, a new review is not feasible at this time. No further activity on this topic will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Screening and Management of Pulmonary Hypertension in Adults with Sickle Cell Disease

Topic #: 0719

Nomination Date: 10/25/2016

Topic Brief Date: 02/16/2017

Authors:
Kara Winchell

Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary of Key Findings:

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review on this topic would not be duplicative of an existing product.
    - A new evidence review examining pulmonary hypertension (PH) in sickle cell disease (SCD) would not be duplicative. We identified one 2016 evidence review examining the threshold at which right heart cardiac catheterization (RHCC) should be recommended after echocardiogram (ECG) to confirm a diagnosis of PH (KQ 2). We identified one Cochrane protocol, which aims to examine interventions to treat PH in the SCD population, including anticoagulants and vasodilators (KQ 4). They plan to examine harms in these interventions as well (KQ 4a). However, this review fails to cover one of the interventions in KQ 4 and 4a (hydroxyurea). No evidence reviews that examine KQs 1 or 3 were identified.

- Impact: The impact potential is high. The standard of care is unclear. Regarding screening for PH in the SCD population, the NHLBI was unable to make a recommendation due to lack of evidence. The NHBLI's recommendation for a RHCC based on high TRJV was only consensus-panel expertise based. There were no recommendations for treatment. Additionally, there is practice variation. Due to insufficient evidence, the clinical practice guidelines are weak, and physicians use personal judgement to determine courses of treatment.

- Feasibility: An AHRQ evidence review is not feasible at this time.
    - *Size/scope of review:* Our search of PubMed for screening and management of PH in SCD resulted in 145 unique titles. Upon title and abstract review of all 145 results, we identified a total of nine studies potentially relevant to the key questions in the nomination. Six published studies were identified for KQ 1a-b (screening and monitoring for PH in cardiovascular [CV] symptomatic and asymptomatic patients), four studies that examine at what tricuspid regurgitant jet velocity (TRJV) during an ECG a RHCC should be used to confirm PH (KQ 2) were identified, no studies cover KQ 3 (regarding at what mean pulmonary arterial pressure [mPAP] by RHCC pharmacologic treatments improves outcomes), one published study examine the benefits of various interventions for PH in adults with SCD (KQ 4), but no studies examine the harms of interventions for PH (KQ 4a).
    - *Clinicaltrials.gov:* We identified no relevant clinical trials.

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Introduction

Pulmonary hypertension (PH) is a common complication associated with Sickle Cell Disease (SCD).[1] Diagnosis of PH can be difficult, due to the large number of common causes for the symptoms of PH, such as dyspnea, pain, and fatigue that often present in the SCD population. Optimal treatment for PH in the SCD population is not well researched, and is often left up to the patient's physician. In order to establish a standard of care, more primary research in the SCD population is required.

Topic nomination 0719 was received on October 25, 2016. It was nominated by the American Society of Hematology (ASH). After consulting with the nominator and narrowing the scope of the nomination to the most important questions, the resultant questions for this nomination are:

Key Question 1. In adults with Sickle Cell Disease (SCD), does screening and monitoring for pulmonary hypertension (PH) reduce cardiovascular (CV) morbidity or mortality in:

a. CV asymptomatic patients
    i. Screening
    ii. Monitoring
b. CV symptomatic patients
    i. Screening
    ii. Monitoring

Key Question 2. In adults with SCD, at what tricuspid regurgitant jet velocity (TRJV) detected during an echocardiogram (ECG) should right heart cardiac catheterization (RHCC) be recommended to confirm a diagnosis of PH?

Key Question 3. In adults with SCD and borderline PH, at what mean pulmonary arterial pressure (mPAP) by RHCC does pharmacologic treatment improve outcomes?

Key Question 4. What is the effectiveness and comparative effectiveness of pharmacologic options (hydroxyurea, anticoagulants, and pulmonary vasodilators) to treat PH in adults with SCD?

a. What are the harms of pharmacologic options to treat PH in adults with SCD?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, and outcomes (PICOs) of interest. See Table 1.

Table 1. Key Questions and PICOTs "

Key Question	1. In adults with SCD, does screening and monitoring for pulmonary hypertension reduce CV morbidity or mortality in: a. CV asymptomatic patients i. Screening ii. Monitoring b. CV symptomatic patients i. Screening ii. Monitoring	2. In adults with SCD, at what TRJV detected during an echo should right heart cardiac catheterization be recommended to confirm a diagnosis of PH?	3. In adults with SCD with borderline PH, at what mPAP by cardiac catheterization does pharmacologic treatment improve outcomes?	4. What is the effectiveness and comparative effectiveness of pharmacologic options (hydroxyurea, anticoagulants, and pulmonary vasodilators) to treat PH in adults with SCD? a. What are the harms of pharmacologic options to treat PH in adults with SCD?
Population	Adults with SCD **and** (a) no cardiopulmonary symptoms, or (b) cardiopulmonary symptoms (eg, dyspnea on exertion, fatigue, chest pain, lower extremity edema, syncope or near-syncope, and palpitations)	Adults with SCD with or without cardiopulmonary symptoms undergoing routine screening echo for PH	Adults with SCD and borderline PH identified by cardiac catheterization	Adults with SCD and PH
Intervention	Echocardiography, spirometry, plethysmography	Right heart cardiac catheterization at specified thresholds	Pharmacologic treatment (Hydroxyurea, anticoagulants, pulmonary vasodilators) at specified thresholds	Hydroxyurea, anticoagulants, pulmonary vasodilators
Comparator	No screening or monitoring	PFTs, NT-pro-BNP, symptomatic treatment	Continued observation	Placebo, no treatment, other active treatment
Outcome	Diagnosis of pulmonary hypertension, reduction in morbidity/mortality	Diagnosis of pulmonary hypertension, reduction in morbidity/mortality	mPAP levels, stroke, heart failure, CVD related morbidity and mortality	Blood pressure, stroke, heart failure, CVD related morbidity and mortality, adverse events

Abbreviations: CV=Cardiovascular; CVD=Cardiovascular Disease; mPAP=Mean Pulmonary Arterial Pressure; NT-pro-BNP=N-Terminal pro B-Type Natriuretic Peptide; PH=Pulmonary Hypertension; PFT=Pulmonary Function Tests; SCD=Sickle Cell Disease; TRJV=Tricuspid Regurgitant Jet Velocity

Methods

To assess topic nomination 0719, *Screening and Management of Pulmonary Hypertension in Sickle Cell Disease,* for priority for a systematic review or other AHRQ EHC report, we used a modified process based on established criteria. Our assessment is hierarchical in nature, with the findings of our assessment determining the need for further evaluation. Details related to our assessment are provided in Appendix A.

1. " Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. " Establish the overall *importance* of a potential topic as representing a health or " healthcare issue in the United States. "
3. " Determine the *desirability of new evidence review* by examining whether a new " systematic review or other AHRQ product would be duplicative. "
4. " Assess the *potential impact* a new systematic review or other AHRQ product.
5. " Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. " Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance (see Appendix A).

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews pertaining to the key questions of the nomination. Table 2 includes the citations for the reviews that were determined to address the key questions.

Impact of a New Evidence Review

The impact of a new evidence review was assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether a new review could influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.). See Appendix A.

Feasibility of New Evidence Review

We conducted a literature search in PubMed from <December 2011 to December 2016.

We reviewed all identified titles and abstracts for inclusion and classified identified studies by study design, to assess the size and scope of a potential evidence review. See *Table 2, Feasibility Column, Size/Scope of Review* for the citations of included studies.

We also searched Clinicaltrials.gov for recently completed or in-process unpublished studies. See Appendix B for the PubMed search strategy and links to the ClinicalTrials.gov search.

Compilation of Findings

We constructed a table outlining the selection criteria as they pertain to this nomination (see Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. According to the CDC, approximately 100,000 Americans have SCD, and pulmonary hypertension is a common comorbidity of the disease.[2]

Desirability of New Review/Duplication

A new evidence review examining screening and management of PH in SCD would not be duplicative. We identified one 2016 evidence review examining the threshold at which right heart cardiac catheterization (RHCC) should be recommended after ECG to confirm a diagnosis of PH (KQ 2).[3] We identified one Cochrane protocol,[4] which aims to examine interventions to treat PH in the SCD population, including anticoagulants and vasodilators (KQ 4). They plan to examine harms in these interventions as well (KQ 4a). However, this review fails to cover one of the interventions in KQ 4 and 4a (hydroxyurea). No evidence reviews that examine KQs 1 or 3 were identified. See *Table 2, Duplication* for the systematic review citations that were determined to address the key questions.

Impact of a New Evidence Review

The nomination has high impact potential. The standard of care is unclear. The National Heart, Lungs, and Blood Institute (NHLBI) published sickle cell guidelines in 2014,[5] which included recommendations about screening and managing pulmonary hypertension. However for the SCD population, the NHLBI was unable to make a screening recommendation due to lack of evidence. The NHBLI's recommendation for a RHCC based on high TRJV was only consensus-panel expertise based. There were no recommendations for treatment. Most pulmonary hypertension guidelines do not include the sickle cell population as a subgroup, so information from an evidence review that results in updated guidelines may be used in multiple PH guidelines. The American Thoracic Society published guidelines in 2014 (approved in October 2013)[1] titled "An Official American Thoracic Society Clinical Practice Guideline: Diagnosis, Risk Stratification, and Management of Pulmonary Hypertension of Sickle Cell Disease." Most of the studies included were greater than five years old. Additionally, there is practice variation. Due to insufficient evidence, the clinical practice guidelines are weak, and physicians use personal judgement to determine course of treatment.

Feasibility of a New Evidence Review

An AHRQ evidence review examining screening and management of pulmonary hypertension in the sickle cell disease population is not feasible at this time. Our five-year search of PubMed for screening and management of PH in SCD resulted in 145 unique titles. Upon title and abstract review of all 145 results, we identified a total of nine studies potentially relevant to the key questions in the nomination.[6-14] Six published studies were identified for KQ 1a-b (screening and monitoring for PH in cardiovascular [CV] symptomatic and asymptomatic patients),[6-11] four studies that examine at what tricuspid regurgitant jet velocity (TRJV) during an echocardiogram (ECG) a right heart cardiac catheterization (RHCC) should be used to confirm PH (KQ 2) were identified,[6,9,12,13] no studies cover KQ 3 (regarding at what mean pulmonary arterial pressure (mPAP) by RHCC pharmacologic treatments improves outcomes), one published study examine the benefits of various interventions for PH in adults with SCD (KQ 4), [14] but no studies examine the harms of interventions for PH (KQ 4a).

We identified no relevant clinical trials. *See Table 2, Feasibility* for all citations that were determined to address the key questions.

Table 2. Key questions with the identified corresponding evidence reviews and original research

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Original Research)
1a.i: Screening for PH in CV asymptomatic patients	None identified	Size/scope of review Relevant Studies: 5 • Prospective Cohort: 1[6] • Case-Control: 1[7] • Longitudinal: 1[8] • Observational: 1[9] • Retrospective Cohort: 1[10]

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Original Research)
1a.ii: Monitoring PH in CV asymptomatic patients	None identified	Size/scope of review Relevant Studies: 1 • Retrospective Cohort: 1[10]
1b.i: Screening for PH in CV symptomatic patients	None identified	Size/scope of review Relevant Studies: 5 • Prospective Cohort: 1[11] • Case-Control: 1[7] • Longitudinal: 1[8] • Observational: 1[9] • Retrospective Cohort: 1[10]
1b.ii: Monitoring PH in CV symptomatic patients	None identified	Size/scope of review Relevant Studies: 1 • Prospective Cohort: 1[11]
2: TRJV for RHCC	Total number of completed or in-process evidence reviews: 1 • Other: 1[3]	Size/scope of review Relevant Studies: 4 • Prospective Cohort: 2[6,12] • Observational: 1[9] • Retrospective Chart Review: 1[13]
3: mPAP by RHCC (pharmacologic treatment)	None identified	None identified.
4: CE and effectiveness of pharmacologic treatment of PH	Total number of completed or in-process evidence reviews: 1 • Cochrane Protocol: 1[4]	Size/scope of review Relevant Studies: 1 • Prospective: 1[14]
4a: Harms of pharmacologic treatment of PH	Total number of completed or in-process evidence reviews: 1 • Cochrane Protocol: 1[4]	None identified.

Abbreviations: CE=Comparative Effectiveness; CV=Cardiovascular; mPAP=Mean Pulmonary Arterial Pressure; PH=Pulmonary Hypertension; RHCC=Right Heart Cardiac Catheterization; TRJV=Tricuspid Regurgitant Jet Velocity

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review on this topic would not be duplicative of an existing product.
    - A new evidence review examining pulmonary hypertension (PH) in sickle cell disease (SCD) would not be duplicative. We identified one 2016 evidence review examining the threshold at which right heart cardiac catheterization (RHCC) should be recommended after echocardiogram (ECG) to confirm a diagnosis of PH (KQ 2). We identified one Cochrane protocol, which aims to examine interventions to treat PH in the SCD population, including anticoagulants and vasodilators (KQ 4). They plan to examine harms in these interventions as well (KQ 4a). However, this review fails to cover one of the interventions in KQ 4 and 4a (hydroxyurea). No evidence reviews that examine KQs 1 or 3 were identified.
- Impact: The standard of care is unclear. Regarding screening for PH in the SCD population, the NHLBI was unable to make a recommendation due to lack of evidence. The NHBLI's recommendation for a RHCC based on high TRJV was only consensus-panel expertise based. There were no recommendations for treatment. Additionally, there is practice variation. Due to insufficient evidence, the clinical practice guidelines are weak, and physicians use personal judgement to determine courses of treatment.

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Appendices

Appendix A: Selection Criteria Summary (

Appendix B: Search Strategy & Results (Feasibility)

Appendix A. Selection Criteria Summary (

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this nomination represents a health care intervention available in the United States.
1b. Is the nomination a request for a systematic review?	Yes, this nomination is a request for an AHRQ systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes, the focus of this nomination is on both effectiveness and comparative effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, this nomination focuses on a biologic plausibility and is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, this nomination represents a significant disease burden. According to the CDC, approximately 100,000 Americans have SCD, and pulmonary hypertension is a common comorbidity of the disease.[2]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this nomination may affect health care decision making and a significant cost for a vulnerable population.
2c. Represents important uncertainty for decision makers	Yes, this nomination represents important uncertainty for decision makers. The current American Thoracic Society[1] and NHLBI guidelines[5] are based on older studies.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination incorporates both benefits and harms of treatments for pulmonary hypertension in the sickle cell disease population.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, this nomination represents a high cost to both health systems and payers.
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	A new evidence review examining screening and management of PH and SCD would not be duplicative. We identified one 2016 evidence review examining the threshold at which right heart cardiac catheterization (RHCC) should be recommended after ECG to confirm a diagnosis of PH (KQ 2).[3] We identified one Cochrane protocol,[4] which aims to examine interventions to treat PH in the SCD population, including anticoagulants and vasodilators (KQ 4). They plan to examine harms in these interventions as well (KQ 4a). However, this review fails to cover one of the interventions in KQ 4 and 4a (hydroxyurea). No evidence reviews that examine KQs 1 or 3 were identified.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be	The standard of care is unclear. Regarding screening for PH in the SCD population, the NHLBI was unable to make a recommendation due to lack of evidence. The NHBLI's

addressed by a new evidence review)?	recommendation for a RHCC based on high TRJV was only consensus-panel expertise based. There were no recommendations for treatment.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	There is practice variation. Due to insufficient evidence, the clinical practice guidelines are weak, and physicians use personal judgement to determine course of treatment.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	An AHRQ evidence review examining screening and management of pulmonary hypertension in the sickle cell disease population is not feasible at this time. *Size/scope of review:* Our search of PubMed for screening and management of PH in SCD resulted in 145 unique titles. Upon title and abstract review of all 145 results, we identified a total of nine studies potentially relevant to the key questions in the nomination.[6-14] Six published studies were identified for KQ 1a-b (screening and monitoring for PH in cardiovascular [CV] symptomatic and asymptomatic patients),[6-11] four studies that examine at what tricuspid regurgitant jet velocity (TRJV) during an echocardiogram (ECG) a right heart cardiac catheterization (RHCC) should be used to confirm PH (KQ 2) were identified,[6,9,12,13] no studies cover KQ 3 (regarding at what mean pulmonary arterial pressure (mPAP) by RHCC pharmacologic treatments improves outcomes), one published study examine the benefits of various interventions for PH in adults with SCD (KQ 4),[14] but no studies examine the harms of interventions for PH. *Clinicaltrials.gov:* We identified no relevant clinical trials.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; CDC=Centers for Disease Control and Prevention; ECG=Echocardiogram; PH=Pulmonary Hypertension; KQ=Key Question; mPAP=Mean Pulmonary Arterial Pressure; RHCC=Right Heart Cardiac Catheterization; SCD=Sickle Cell Disease; TRJV=Tricuspid Regurgitant Jet Velocity

Appendix B. Search Strategy & Results (Feasibility)

Topic: Screening and Management of Pulmonary Hypertension in Adults with Sickle Cell Disease Date: December 1, 2016 Database Searched: MEDLINE (PubMed)	
Concept	Search String
Sickle Cell	(("Sickle Cell Trait"[Mesh] OR "Anemia, Sickle Cell"[Mesh] OR "Hemoglobin SC Disease"[Mesh])) OR (("sickle cell"[Title/Abstract] OR "hemoglobin S"[Title/Abstract]))
AND	
Pulmonary Hypertension #28 N=42786	("Hypertension, Pulmonary"[Mesh]) OR ((("pulmonary hypertension"[Title/Abstract] OR "pulmonary arterial hypertension"[Title/Abstract])) OR ("high blood pressure"[Title/Abstract] AND lungs[Title/Abstract]))
OR	
Drugs used for pulmonary hypertension in sickle cell	(("Hydroxyurea"[Mesh]) OR ("Anticoagulants"[Mesh] OR "Anticoagulants" [Pharmacological Action])) OR ("Vasodilator Agents"[Mesh] OR "Vasodilator Agents" [Pharmacological Action])
AND	
Sickle Cell OR Pulmonary Hypertension	((("Hypertension, Pulmonary"[Mesh]) OR ((("pulmonary hypertension"[Title/Abstract] OR "pulmonary arterial hypertension"[Title/Abstract])) OR ("high blood pressure"[Title/Abstract] AND lungs[Title/Abstract]))))) OR ((("Sickle Cell Trait"[Mesh] OR "Anemia, Sickle Cell"[Mesh] OR "Hemoglobin SC Disease"[Mesh])) OR (("sickle cell"[Title/Abstract] OR "hemoglobin S"[Title/Abstract])))
#36 N=7980	
NOT	
Not Editorials, etc.	((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type]
Limit to last 5 years ; human ; English ; Adult	Filters activated: published in the last 5 years, Humans, English, Adult: 19+ years.
N=145	
Systematic Review N=10	PubMed subsection “Systematic [sb]”
Randomized Controlled Trials N=105	Cochrane Sensitive Search Strategy for RCT’s “(((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt])”
Other N=140	

Clinicaltrials.gov
6 studies found for: sickle | pulmonary hypertension | Studies received from 11/22/2011 to 11/28/2016

https://clinicaltrials.gov/ct2/results?term=sickle&type=&rslt=&recr=&age_v=&gndr=&cond=pulmonary+hypertension&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=11%2F22%2F2011&rcv_e=11%2F28%2F2016&lup_s=&lup_e=